CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-612

MEDICAL REVIEW(S)

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Medical Officer's Review of NDA 20-612
Original

APR 10 1997

NDA # 20-612
M.O. Review #1

Submission: 6/11/96
Review completed: 10/11/96

Drug name:	Lidocaine U.S.P.
Generic name:	Lidocaine Patch, 5% w/w
Proposed trade name:	Lidoderm™ Patch
Chemical name:	2-(diethylamino)-N-(2,6-dimethylphenyl) Acetamide
Sponsor:	Hind Health Care, Inc. 165 Gibraltar Court Sunnyvale, CA 94089 Tel.:(408)747-1765
Pharmacologic Category:	Local Anesthetic
Proposed Indication:	Treatment of pain from post-herpetic neuralgia.
Dosage Form(s):	Adhesive Patch
Route of Administration:	Topical, Dermal
NDA Drug Classification:	3S
Related Drugs:	Lidocaine gel
Related Reviews:	Statistical Review: pending Chemistry Review: pending Pharmacokinetic Review: pending Pharmacology-Toxicology: pending

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3 Material Reviewed

NDA 20-612: Volumes 2.1 thru 2.10, 2.11, 2.12,2.13, 2.44, 2.46, 2.49, 2.65, 2.69. 2.73, 2.79, 2.86, 2.91, and 2.97. The Annual Report for IND [ ] Lidoderm™Patch dated 9/10/96 and the annual report for IND Lidoderm™Gel dated 9/10/96 were also reviewed.

4 Chemistry/Manufacturing Controls

The chemistry review for this application is pending. Numerous deficiencies were noted on the environmental assessment report . The sponsor has been notified of these deficiencies and is currently trying to correct them.

5 Animal Pharmacology/Toxicology

The pharmacology review for this application is pending.

6 Clinical Background

6.1 Relevant human experience

As of the filing of this NDA submission, a total of 699 patients have been treated in clinical trials conducted in the U.S. with the Lidoderm™ Patch. A patch-delivery system different from the one under review that contains 3% lidocaine, is available as an over-the-counter (OTC) product in the U.S. The Sponsor of the OTC product is different than the one who submitted this NDA application. To this reviewer's knowledge there have not been any potential or real health hazards reported associated with the use of the OTC 3% lidocaine patch. The Sponsor of this application is also conducting a Phase 3 clinical trial in post-herpetic neuralgia (PHN) patients where the Lidoderm™ Patch can not be used due to body topography problems (i.e., face and neck regions) utilizing a gel containing 5% lidocaine under IND Lidoderm™Gel. Use of the 5% Lidoderm™Gel has been associated with a higher incidence of reports of dermal irritancy than with the patch formulation. The Sponsor is still in the process of recruiting patients to complete the Phase 3 PHN trial for Lidoderm™Gel.

There are other strengths and formulations of topical lidocaine containing products that have been approved and are marketed in the U.S. The last one approved by this reviewing division was EMLA™Cream, which is a eutectic mixture of lidocaine 2.5% and prilocaine 2.5%, indicated for use as a topical anesthetic for local analgesia. Thus far, no unrecognized risk for a significant health hazard has arisen with the use of EMLA™Cream since it has been marketed.

6.2 Important information from related INDs and NDAs

Pursuant to obtaining agency marketing approval for their proposed indication, the Sponsor applied for and was granted orphan designation (application #95-923) for the Lidoderm™ Patch (lidocaine patch 5%) to be used in the treatment and

management of post-herpetic neuralgia (PHN) by the FDA's Office of Orphan Drug Products (HFD-35). Although the Sponsor is currently conducting clinical trials with the Lidoderm™ Patch for other indications, they have not generated sufficient data to apply for indications other than PHN at the time of filing of this submission.

6.3 Foreign experience

The Sponsor of this application, Hind Health Care, Inc., is not involved in the foreign marketing of this drug.

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

The biopharmaceutics review for this application is pending.

6.5 Other relevant background information

Lidocaine is an amide-type local anesthetic agent. Lidoderm™ Patch usually causes dermal analgesia within 1 hour of its application. The duration of analgesia is dependent on patch wearing time. The mechanism of action via which lidocaine exerts its anesthetic properties is thought to be related to the drug's ability to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses. The Sponsor postulates that the Lidoderm™ Patch (lidocaine 5%) when applied to intact skin, causes dermal analgesia by the release of lidocaine from the patch into the epidermal and dermal layers of the skin where the drug accumulates and selectively acts on a-delta and c-fiber function of dermal pain receptors and nerve endings. The Sponsor was able to demonstrate in clinical trials, via quantitative thermal sensory testing using a Marstock apparatus which tests the function of these 2 types of skin sensory nerve fibers, that the drug lowers the threshold for cold pain and cold perception, while it generally fails to affect the threshold for heat pain, heat perception and touch perception.

6.6 Directions for Use

The Sponsor's proposed recommendations for usage of the Lidoderm™ Patch are as follows: the patch should be applied once a day to the affected painful area of skin for up to 12 hours within a 24-hour period. Patches may be cut into smaller sizes with scissors prior to removal of the release liner. No more than 3 Lidoderm™ Patches may be used at any one time and should not be applied over areas larger than 420 cm^2 (70 in^2). Clothing may be worn over the area of application.

7 Description of Clinical Data Sources

The data for this NDA review was compiled and submitted by the Sponsor. The Sponsor conducted all of the U.S. IND clinical efficacy and safety trials but used [redacted] to conducted the dermal safety studies.

8 Clinical Studies

This NDA submission contains data supplied by the Sponsor from 9 trials. All nine trials were conducted under the drug's IND. Three out of the 9 trials are pharmacokinetic studies. *(See the PK review for further information about these trials.)* Of the remaining 6 trials, 3 are clinical efficacy and safety studies in post-herpetic neuralgia (PHN) and venepuncture, 2 are contact irritancy trials, and 1 is a photosensitivity study. Of the 2 clinical efficacy and safety studies in PHN, one is the pivotal Phase 3 trial the Sponsor conducted for the proposed indication, while the other is a small, Phase 2 trial which was the basis for the design and plan of the larger, Phase 3 trial. These 2 trials, are discussed in detail along with the venepuncture trial in the efficacy portion of this review. The 3 dermal safety trials, which followed standardized protocols, are required to document a topical drug's safety profile. They are briefly discussed in the Special Studies subsection of the safety review. *(See Section 10.2.3 Special Studies.)*

8.1 Indication

The Sponsor proposes that the Lidoderm™ Patch be indicated for the relief of acute allodynia (painful hypersensitivity), and the chronic pain associated with post-herpetic neuralgia (PHN).

8.1.1 Reviewer's Trial #1

Title: A Multicenter, Randomized, Double-Blind Study of the Analgesic Efficacy and Safety During 30 Days of as Needed Use of Topical Lidoderm™ Patches in Patients with Post-Herpetic Neuralgia.

8.1.1.1 Objective/Rationale

The objectives of this trial were twofold:

1. To evaluate the analgesic efficacy of the Lidoderm™ Patch when applied to the area of maximally painful skin in patients with post-herpetic neuralgia (PHN).
2. To evaluate both the local and systemic safety profile of the Lidoderm™ Patch in patients with PHN.

8.1.1.2 Design

This was a 30-day, multicenter, double-blind, placebo-controlled, randomized, parallel-design trial conducted at 2 academic, out-patient pain clinics in the United States in patients with post-herpetic neuralgia (PHN) located on the torso or limbs. Patients underwent 2 treatment sessions in the clinic that were at least 48 hours apart where test patches were applied to PHN-skin for a period of 10 hours. The patients went on to complete a home-use study phase of 21-28 days duration during which they were permitted to use up to 3 patches per day for a maximum of 12 hours in a 24-hour period. Upon completion of this home-use phase, the patients returned to the clinic for

their final study visit where they were given the option of participating in an open-label trial with the Lidoderm™ Patch to assess long-term safety associated with continuous patch use.

8.1.1.3 Protocol

Potential patients, who were recruited from local news and media coverage or referred by their physicians to the universities' pain management clinics, were initially screened via questionnaire and review of medical records for trial eligibility. In order to be eligible for trial entry, patients had to have a diagnosis of PHN, which was defined in the trial protocol as pain persisting or arising in areas that had been previously affected by a localized herpes zoster infection (shingles) for more than 1 month antecedent to the healing of the skin lesions. The diagnosis of PHN had to be confirmed by a review of available medical records documenting an episode of herpes zoster (HZ) infection as well as a neurosensory physical exam of the affected area. There could be no signs of skin breakdown, inflammation or incomplete healing post-HZ infection present at the baseline visit. Evidence of another cause of pain within the area affected, or the presence of another pain condition of equal or greater intensity than PHN were reasons for exclusion from the trial. Patients who had neurological findings of spinal cord damage due to HZ , or who had undergone ablative neurosurgical procedures or nerve blocks as part of pain management of PHN were also ineligible for trial entry. In addition, study subjects had to be 21 years or older, in good physical health, without a history of allergy to lidocaine or amide-type local anesthetic drugs, and using an acceptable form of contraception if they were of child bearing potential.

Potential patients were initially evaluated at the pain clinics where the trial was conducted. The initial visit was comprised of a verbal description by the patient of the quality and location of their pain, a patient' s global pain rating via a 100 mm visual analog scale (VAS), a PHN Pain Questionnaire that included historical, clinical and anatomical aspects of the neuralgia and treatment interventions previously tried, and a neurological exam by the trial investigator's to screen for other pain conditions and mental impairment which could interfere with patients' participating in the trial. A sensory exam was also performed by the trial investigators which included delineation or mapping of the areas of pain, allodynia and sensory loss. Subjects who met inclusion criteria for trial entry and wished to continue, were assigned a patient number after they had signed an informed consent. For the 5 days prior to the baseline visit, patients kept a daily pain diary which consisted of a 100 mm global visual analogue scale (VAS) rating of pain intensity and a log of analgesic medications used that day.

The trial was comprised of 3 clinical visits conducted at the pain clinics' labs and a 21-28 day at home-use phase of the test patch. Sessions 1 and 2 were similar in scope, and were completed within 48 hours of each other. Session 3 was the final study visit and was conducted after the patients had completed the home-use period. The 2 clinical lab sessions took 6 hours to complete and were organized as follows:

Baseline measures: 100 mm VAS for Pain (x 2 administered 15 minutes apart)
Symptom Checklist
Allodynia Severity Rating
Sensory Examination of Area of Pain
Inspection of Affected Skin
Skin Mapping
Quantitative Thermal Sensory Testing (QST) - optional

Patch application: Up to 3 patches were then applied to the area of maximum pain, enough to completely cover the area of painful skin. Test article application was time zero.

1, 2, 4, 6-hour ratings: 100 mm VAS for Pain
Symptom Checklist
Category Pain Relief (0-5)

After 6 hours of test article application, the patches were removed and the following tests were repeated:

Allodynia Severity Rating
Sensory Examination of Area of Pain
Quantitative Thermal Sensory Testing (QST) - optional

The same patches were then reapplied to the test area. The patients then returned home where they completed the rest of the session(s):

8 and 10-hour rating: 100 mm VAS for Pain
Symptom Checklist
Category Pain Relief (O-5)

The test patches were then removed following the 10-hour rating. Over the next 21-28 days, the patients used the test patches at home. The frequency of use was at the discretion each patient with the proviso that they did not wear the patch(es) for more than 12 hours in a 24-hour period. Patients were allowed during this phase to use up to 3 patches per session. The use of medicated creams, ointments or gels such as capsaicin were not permitted in conjunction with the test patch, but patients were allowed to apply non-medicated moisturizers to the test area between treatment sessions. During the at home-use phase, patients were required to keep a daily log which contained the following: time of patch application and removal, a global rating of the average pain intensity for that day, and a listing of the analgesic medications used that day. The use of concomitant medications for PHN was to remain constant for the duration of the study. Monitoring for drug-related adverse events and compliance during the at home-use phase of the trial was accomplished by weekly phone calls from the

study coordinator to the participating subjects.

Session 3, the final study visit, was completed after the home use phase of the test patches. Patients applied the test patch(es) 4 hours prior to undergoing the following tests at the pain clinics:

100 mm VAS for Pain
Category Relief Scale (0-5)
Symptom Checklist
Sensory Examination of Area of Pain
Inspection of Affected Skin
Skin Mapping
Quantitative Thermal Sensory Testing (QST) - optional

All unused test patches were collected as were daily patient diaries at this final visit. Quantitative Thermal Sensory Testing (QST) was done only during Sessions 1 and 3 to patients at the discretion of the investigators. Blood samples for lidocaine levels were drawn at pre-application, and 6 hours post-application at Session 2, and 4 hours post-application at Session 3.

Upon completion of the trial, patients were given the option of open-label use of the Lidoderm™ Patch following a 1-week washout period, if they agreed to 3 follow-up visits per year for safety and efficacy monitoring.

8.1.1.3.1 Population

A total of 171 patients were enrolled from the 2 study sites into the trial. (See Table 1 below.)

Table 1 - Investigator Sites and Number of Patients Entered and Evaluable

Investigator/Site	Study Site Number	Total Enrolled	Total Evaluable
Michael Rowbotham, MD Pain Center Research Clinic University of California 2233 Post Street, Suite 104 San Francisco, CA 94115	01	84	74
Bradley Galer, MD Multidisciplinary Pain Center University of Washington School of Medicine, XD-45 4245 Roosevelt Way N.E. Seattle, WA 98105	02	87	76

Ten (10) out of the 171 patients enrolled in the trial were discontinued before study medications were dispensed: 4 patients prior to being randomized to a treatment group, 2 patients randomized to the Lidoderm™ Patch group, and 4 patients randomized to the placebo patch group. A summary of the demographic characteristics of the 150 evaluable patients enrolled in the trial is presented in Table 2. (See below.)

The 2 treatment groups were similar in their demographic compositions for age, gender, weight, race, duration of disease and daily occurrence of pain. The average age of the evaluable patients was 74.2 years, the majority of whom were female (57%) and caucasian (91%), with a mean weight of 154.4 lbs., and a mean duration of disease of 3.5 years. (See Table 2 below.)

Table 2 - Demographic and Subject Characteristics of Patients Entered in the Trial

Characteristic	Placebo Patch	Active Patch	Total	P-Value
Number Entered	50	100	150	
Age: (years)				
Mean±SD	73.70±8.05	74.37±6.79	74.15±7.21	0.601[a]
Range	47.0-88.0	50.0-92.0	47.0-92.0	
Sex: (%)				
Male	20(40%)	44(44%)	64(43%)	0.653[b]
Female	30(60%)	56(56%)	86(57%)	
Race:				
Caucasian	46(92%)	91(91%)	137(91%)	0.867[b]
Black	0(0%)	1(1%)	1(1%)	
Hispanic	0(0%)	1(1%)	1(1%)	
Asian	4(8%)	7(7%)	11(7%)	
Weight: (lbs)				
Mean±SD	151.95±28.76	155.56±35.77	154.35±33.52	0.539[a]
Range	93.0-220.0	83.0-321.0	83.0-321.0	
Duration of Disease:				
Mean±SD(yrs.)	4.45±4.46	3.09±3.22	3.54±3.72	0.038[a]
Range	0.0±20.0	0.0-16.0	0.0±20.0	
Pain from PHN Every Day?				
Yes	49(100%)	100(100%)	149(100%)	1.000[b]
No	0(0%)	0(0%)	0(0%)	
Not Reported	1	0	1	

[a] P-values for treatment comparison from two-way analysis of variance with factors of treatment and site.
[b] P-values from Cochran-Mantel-Haenszel test for general association (controlling for investigator). For the variable race, the p-value was calculated after collapsing the categories into caucasian and non-caucasian.
[c] PHN represents post-herpetic neuralgia.

Table 2 - Demographic and Subject Characteristics of Patients Entered in the Trial (Cont.)

Characteristic	Placebo Patch	Active Patch	Total	P-Value
Number Entered	50	100	150	
Ave. Daily PHN Pain:				
Faint	0(0%)	0(0%)	0(0%)	0.437[b]
Mild	2(4%)	1(1%)	3(2%)	
Moderate	13(27%)	21(21%)	34(23%)	
Strong	24(49%)	58(58%)	82(55%)	
Intense	10(20%)	91(91%)	137(91%)	
Not Reported	1	0	1	
Skin Surface Painfully Sensitive?				
Yes	46(94%)	92(93%)	138(93%)	0.832[b]
No	3(6%)	7(7%)	10(7%)	
Not Reported	1	1	2	
Pre-Session Pain Intensity (VAS)				
Mean±SD	61.40±17.06	63.05±15.45	62.50±15.97	0.525[a]
Range	21.0-96.2	20.6-98.8	20.6-98.8	

[a]P-values for treatment comparison from two-way analysis of variance with factors of treatment and site.
[b]P-values from Cochran-Mantel-Haenszel test for general association (controlling for investigator). For the variable race, the p-value was calculated after collapsing the categories into caucasian and non-caucasian.
[c]PHN represents post-herpetic neuralgia.

8.1.1.3.2 Endpoints

There were 3 primary efficacy variables evaluated in this trial: patient self-assessment of magnitude of pain via a 100 mm visual analog scale (VAS), patient self-assessment of pain relief via a categorical relief scale (0-5), and investigator's sensory skin testing (allodynia). Quantitative Thermal Sensory Testing (QST) was done on select patients at the discretion of the investigators for investigational research purposes.

Safety was evaluated via the following: monitoring of systemic lidocaine blood levels following 6 hours of patch-use, patient's self-reporting of symptoms via a 27-item side-effects check list, and skin examinations of the area treated.

8.1.1.3.3 Statistical considerations

Sample size calculations for the number of subjects needed for a parallel-trial design with a type I error of less than 5% powered at 0.80 or better were based on power calculations from data generated from the Phase II lidocaine patch trial done under IND and the lidocaine gel study done under IND . The Sponsor also plotted a power curve of randomization ratios to determine which ratio allowed for the maximum exposure of subjects to active patch in a parallel trial design. It was noted by the Sponsor that a 2:1 ratio of active:placebo drug assignment was nearly equivalent in power to a 1:1 randomization ratio, but the former would allow more

subjects to be exposed to the active drug for the safety/toxicity evaluation for this orphan indication.

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

Twenty-one (21) out of the 171 patients enrolled in the trial were discontinued prematurely. Ten out of these 21 patients who had been assigned study numbers were dropped from the trial before study medications had been dispensed for a variety of reasons. (See Table 3 below.) They were dropped for the following reasons: 3 changed their minds, 1 refused to sign consent, 1 decided to try another experimental treatment, 1 suffered from cognitive impairment that prevent participation in the trial, 1 cancelled sessions, 1 had a remission in allodynia, and 1 potential subject died due to cardiac failure.

The primary reasons for the remaining 11 patients who failed to complete the trial are summarized in the following table, Table 3 (see below). The distribution of premature drop-outs was similar for both treatment groups. There was only 1 patient (Patient #414) who was discontinued from the trial due to an adverse drug reaction (i.e., rash at the site of the patch) attributable to the active study medication. There were 2 patients (Patients #119 and #392) who were discontinued from the trial due to mechanical problems with the test vehicle (i.e., the patches failed to stick to their affected skin located on the neck). The one death that occurred during this trial in a patient (Patient #107) treated with the active patch who had a prior history of heart disease was attributable to cardiac failure and will be discussed in detail later in the safety review. The other premature discontinuation case that will be discussed in detail the safety review involved a patient (Patient #190) who was discontinued from the study after he fell and fractured his hip following a treatment session with the placebo patch. Of the remaining 6 patients, 1 patient (Patient #394) was dropped from the study due to spontaneous improvement in allodynia, 3 patients (Patients #101, #346 and #378) were dropped due to noncompliance, and 2 patients (Patients #317 and #205) were dropped due to other reasons (i.e., difficulty quantifying pain due to memory problems and lost diary cards respectively).

Reviewer's Comments: Upon review of the 3 cases attributed to non-compliance, this reviewer thinks that 2 of the 3 cases (Patients #101 and #378) should be reclassified as lack of efficacy and/or protocol violations. Patient #101 restarted 2 background anticonvulsants above recommended levels due to uncontrolled pain despite being told that this was not permitted while participating in the study. The other case, Patient #378, failed to disclose to the investigator re: a pre-existing chronic pain syndrome located in the same area that was being studied due to desperation since multiple other treatment modalities had failed. Reclassifying either case would not impact on the trial's final results.)

Table 3 - Summary of Primary Reasons for Premature Discontinuation From the Double-Blind, Placebo-Controlled, Parallel-Group Trial

	Never Assigned	Placebo	Active	Total
Patient Enrolled	4	57	110	171
Excluded from Safety				
Never Used Patches[a]	4	4	2	10
Patients Evaluable for Safety		53	108	161
Excluded from Efficacy				
Reassigned to Lidocaine Gel[b]		1	1	2
Patient Expired[c]		0	1	1
Accidental Injury[d]		1	0	1
Developed Side Effect[e]		0	1	1
Voluntarily Withdrew[f]		0	1	1
Non-Compliant[g]		1	2	3
Other[h]		0	2	2
Patients Evaluable for Efficacy		50	100	150

[a] Patients #115, #194, #207, #348, #370, #376, #387, #408, #411, and #418 never applied study patches.

[b] Patients #119 and #392 were reassigned to gel, since patches would not stick to the neck.

[c] Patient #107 expired due to cardiac failure.

[d] Patient #190 fell down and fractured left hip.

[e] Patient #414 developed a rash after using the patches at session 1.

[f] Patient #394 dropped due to decreased allodynia.

[g] Patient #101 restarted 2 anticonvulsants at dangerous levels. Patient #346 did not show up for session 3 even when rescheduled. Patient #378 failed to mention a 40 year pre-existing pain problem in the same region.

[h] Patient #317 dropped at session 2 due to memory problems and difficulty quantifying her pain. Patient #205 lost the home use diaries.